Metastatic colorectal cancer is the most frequent gastrointestinal malignancy. During the past two decades, overall survival (OS) times have been prolonged from a median of 12 months to up to 30 months in molecularly defined subgroups (1). These advantages have been possible due to the development and introduction of new chemotherapeutic substances, such as irinotecan and oxaliplatin. For more than a decade, drugs targeting specific pathways important for carcinogenesis, metastasis, proliferation, and angiogenesis have further increased the outcome of patients with metastatic colorectal cancer. The use of mAbs targeting EGFR is an established strategy to treat patients with metastatic colorectal cancer and has been shown to improve tumor response, progression-free survival (PFS), and OS when added to standard chemotherapy. In first-line treatment of RAS wild-type tumors, cetuximab and panitumumab are approved and established in combination with FOLFOX or FOLFIRI.

In this issue of Cancer Discovery, Dienstmann and colleagues (2) publish phase I data of Sym004, a mixture of two chimeric human–mouse antibodies targeting two different epitopes of the extracellular domain of EGFR, for the treatment of patients with metastatic colorectal cancer pretreated with anti-EGFR antibodies. In addition, preclinical data demonstrate a superior antitumor effect of Sym004 in comparison with cetuximab that was specifically evident in cells showing EGFR ligand–dependent growth. However, the underlying mechanism of action is not new, and side effects restricting the use of anti-EGFR treatment, such as acneiform exanthema Common Toxicity Criteria Adverse Events (CTC AE) grade 3, occurred in both of the tested dosages in more than 60% of the patients with no advantage in the lower, 9-mg, dose. A recommended dosage for a potential phase II trial has not been evaluated by the investigators of Sym004. Given that two established EGFR-directed antibodies are presently available, the question arises of whether an anti-EGFR antibody (mixture), such as Sym004, with potentially higher side effects is needed, or whether a further molecular subselection of patients is more useful to extend treatment efficacy.

Cetuximab is a monoclonal chimeric (mouse–human) IgG1 antibody targeting the domain III of the extracellular part of the EGFR (3), whereas panitumumab is a fully human IgG2κ antibody binding to slightly different epitopes of the extracellular domain of the EGFR (3). Both antibodies are approved in first-line and further-line treatment of colorectal cancer in combination with FOLFOX or FOLFIRI and as monotherapy (4–6). In 2006, it had become clear that only patients without KRAS exon 2 mutations benefit from anti-EGFR treatment (7). Data of the PRIME and FIRE-3 studies established extended RAS mutational analysis, including KRAS exons 2 and 3, as well as NRAS exons 2, 3, and 4, as today’s standard before any anti-EGFR treatment in metastatic colorectal cancer (6, 8). Within the subgroup of RAS wild-type tumors, tumor response rates of more than 70%, median PFS times of about 10 months, and median survival times beyond 30 months can be reached in first-line treatment (1, 8). In later treatment lines, significant benefits were reached by the combined use of irinotecan plus cetuximab with regard to OS (HR, 0.55; ref. 9) and by monotherapy with panitumumab with regard to PFS (HR, 0.54; ref. 10). Clearly, the advantage of Sym004 in this setting needs to be defined, optimally by head-to-head comparisons with the established antibodies.

To further optimize treatment outcome in the RAS wild-type population and to exploit the full potential of the anti-EGFR strategy in metastatic colorectal cancer, multiple strategies are under investigation. A dose-escalation study (11) to evaluate the feasibility and efficacy of ascending doses of cetuximab until an acneiform exanthema of CTC AE grade 2 or higher is reached in individual patients is presently ongoing. The rechallenge and reexposition of patients to anti-EGFR treatment in later lines is currently under investigation, as it has shown promising results in a small single-center study (12). The molecular subtyping of metastatic colorectal cancer beyond RAS testing to better define the subgroups of patients or tumors responding to anti-EGFR antibodies is being performed within the translational program of several studies. An advanced mutational analysis to test for multiple mutations within the EGFR pathway has become more feasible with next-generation sequencing technology and is becoming available to an increased extent in high-volume centers. Prospective evaluation of EGFR ligand expression, such as...
amphiregulin (AREG) and epiregulin (EREG) is developing as another important field of research. With these data available, the first clinical studies investigating the use of anti-EGFR antibodies in BRAF- and/or PIK3CA-mutated tumors in combination with BRAF inhibitors and/or PI3K inhibitors have shown promising results in early clinical development (13).

Preclinical data on Sym004 show activity in cell lines with high EREG or AREG expression levels. However, other mechanisms of secondary resistance also need to be taken into account to define the patient population potentially benefiting from Sym004. Among those are the recently discovered EGFR mutations, such as S468R, that can cause cetuximab resistance, but will not affect panitumumab efficacy. Also, an increased recycling of the EGFR after cetuximab binding may contribute to resistance; in this context, the clinical relevance of enhanced EGFR degradation induced by Sym004 needs to be clarified. Other mechanisms of resistance, such as further mutations within the intracellular EGFR-dependent signal transduction or the upregulation of alternative growth factor-dependent pathways such as VEGF, TGFα, and c-MET, are most likely not affected by Sym004 (Fig. 1). In this context, it is of interest that only BRAF, RAS, or PIK3CA wild-type tumors showed an objective tumor response when treated with Sym004 (2). The patient population eligible for anti-EGFR treatment most probably won’t be increased by Sym004 when compared with panitumumab or cetuximab.

Typical side effects of cetuximab and panitumumab are skin toxicity and hypomagnesaemia. These side effects were observed at a markedly higher rate with Sym004 and were dose limiting in the phase I trial (2).

To summarize, Sym004 is an additional substance targeting the EGFR in metastatic colorectal cancer and appears to be effective in tumors dependent on the EGFR pathway. As two antibodies are already approved in this setting, the advantage of Sym004 may be to overcome some of the known mechanisms of anti-EGFR resistance. Further studies need to clarify if this advantage, observed in pretreated patients initially responsive to anti-EGFR therapy, outweighs the potentially higher toxicity.

**Disclosure of Potential Conflicts of Interest**

S. Stintzing has received speakers bureau honoraria from Amgen, Bayer, Merck Serono, Roche AG, and Sanofi and is a consultant/advisory board member for Amgen and Merck Serono. V. Heinemann has received speakers bureau honoraria from Amgen, Celgene, Lilly, Merck, Roche, and Sanofi and is a consultant/advisory board member for Amgen, Celgene, Lilly, Merck, Roche, and Sanofi.

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